## STUDIES OF NEPHRITIS.[1]

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(From the Medical Clinic of the Peter Bent Brigham Hospital.)

During the past year and a half in the medical clinic of the Peter Bent Brigham Hospital we have been studying cases of chronic nephritis from several angles. Some of these studies have been published, others are ready for publication, while still others are incomplete. All these studies are more or less closely related to each other and form part of a somewhat systematic investigation of nephritis. Different members of the staff have taken up the study of special phases of the subject, and from time to time each has published the study which he has made. What we will present here represents part of our recent work. The several names that appear under the title are those of the men responsible for the work which is outlined here. In more detailed form each man will publish subsequently under his own name his own work.

A. Test Renal Meals in Relation to Renal Function. The ability of the kidney to excrete certain factors in the average normal diet has been utilized by many as a means of measuring renal function. The excretion of water, sodium chloride, and nitrogen has been tested by most observers. One method suggested by v. Monakow[2] has been to place the patient upon some form of diet which contains daily approximately the same amounts of sodium chloride, nitrogen, and water with a caloric value varying but little from day to day. In relation to this diet the twenty-four-hour amount of urine and its sodium chloride and nitrogen content have been quantitated. Then on different days these patients have received, in addition to the diet, 20 gm. of urea or 10 gm. of sodium chloride, and the ability of the kidney to excrete these added amounts of nitrogen and sodium chloride has been determined.

As in this test it is necessary for the patient to reach a certain degree of equilibrium of excretion after the diet has been begun before the added salt and nitrogen can be given, and as it is necessary to observe the excretion of these substances for at least two days after each is given, and as it is usual to allow the effect of the added amount of the one to end before adding the other, to carry

[1] Presented at a meeting of the Association of American Physicians, held in Washington, D. C., May 11–13, 1915.

[2] Deutsch. Arch. f. klin. Med., 1911, cii, 248.

out this test satisfactorily requires about ten days of accurate dieting with the patient in the hospital.

In 1914 Hedinger and Schlayer[3] published a paper in which the effect of diet on the excretion of water and sodium chloride was studied by submitting the patient for one day to a diet in which different meals contained varying amounts of water, sodium chloride, and nitrogen.[4] The urine was collected in two-hour periods through the day, and the water and sodium chloride were quantitated in each two-hour amount. The test renal meal day was preceded by two days on which the patient was on a light mixed diet containing from 8 to 12 gm. of NaCl, and with a fixed quantity of fluid, and

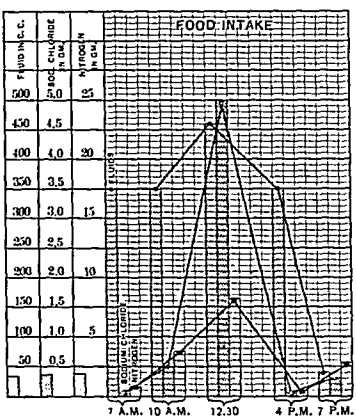


CHART I.—To show amounts of fluid, sodium chloride, and nitrogen in each meal of the renal diet. The lines connecting the tops of the columns give the curve of variation in intake of each constituent.

on these days merely the excretion of water in relation to fluid intake was measured.

This form of test renal meals requires three days of the patient's stay in the hospital, but only on one day is accurate dieting necessary. The question naturally arises. Can as much information be obtained from the one test as from the other? If so, the shorter period of time required for the test of Hedinger and Schlayer would have a manifest advantage. During the past year we have

[3] Deutsch. Arch. f. klin. Med., 1914, cxiv, 120.

[4] In these meals the content of each also varied in food substances having a diuretic effect (water, salt, purins, etc.)

investigated this question. We have modified the test as proposed by Hedinger and Schlayer by quantitating the nitrogen in the various portions as well as the water and sodium chloride, and we have changed slightly the composition of the meals on both the test day (Chart I) and on the two preceding days.[5]

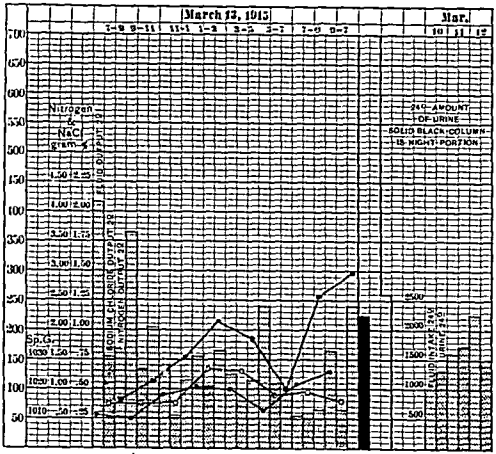


CHART II, Case I.—The series of columns beginning at the left give the amount of urine, sodium chloride, and nitrogen in each two-hour portion from 7 A.M. to 9 P.M., and in the portion from 9 P.M. to 7 A.M. The solid lines joining dots in the space of each column give the specific gravity of the urine and the percentage concentration of sodium chloride and nitrogen. Next is indicated the night portion of urine in relation to the total twenty-four-hour amount. The columns at the right give the fluid intake and urine output in the days preceding the test day.

Without entering at this time into any discussion as to the value of such test renal meals in determining the renal function, we will discuss comparatively the results obtained in the two forms of tests

[5] On the test day we have used the following menu for the several meals:
7 A.M. Coffee, milk, sugar, toast, and butter.
10 A.M. Milk, toast and butter.
12.30 P.M. Bouillon, broiled steak, butter, mashed potato, butter, toast and butter, coffee, milk and sugar.
4 P.M. Tea, milk, sugar, crackers.
7 P.M. Soft egg, blanc mange (one egg, sugar, corn starch, milk) cream, in amount to give approximately total calories 2500, total fluids, 1550 c.c., total protein 76 gm., total fats 127 gm., total carbohydrates, 245 gm., total sodium chloride, 5.8 gm. On the two days preceding the test day the patient usually has a diet containing 2000 calories, 75 gm. of protein, and 4 gm. of sodium chloride.

carried out on the same patient. On sixteen patients with chronic nephritis both tests were carried out in a complete form. In addition to these patients a variety of other methods of testing renal function were applied. In an equal number of cases only the Hedinger and Schlayer test renal meal method was applied in connection with other forms of renal functional tests. The results of all of these tests from the point of view of estimating the function of the kidney and the relative value of each will be discussed by Dr. O'Hare when he publishes a detailed statement of this work.

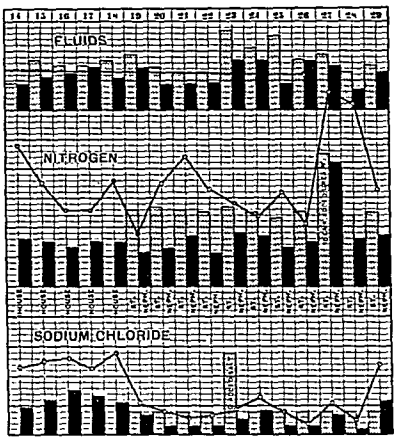


CHART III, Case I.—The hatched columns indicate intake; the solid columns output. The upper series are for fluids, the middle for nitrogen, and the lower for sodium chloride. The added salt and added urea are indicated by the lengthening of the columns of intake.[6]

We have found that these two forms of testing renal function in relation to test diets agree quite well in their results. (Case I, Chart II and III; Case II, Chart IV, and V; Case III, Chart VI and VII; Case IV, Chart VIII and IX). That the results very closely agree in any quantitative sense is, of course, not to be expected, for we have found that if we gave added salt or added urea on several occasions to our patients on a standard diet the results obtained are rarely quantitatively identical, but there is

[6] "House" indicates a general mixed diet; "St. neph." indicates a diet of about 2000 calories, containing 75 gm. of protein and 4 gm. of sodium chloride.

generally a striking similarity in the results from period to period. (Charts VII and XII.)

In the same way we have repeated the Hedinger and Schlayer test renal meal on the same patient and found very considerable variations in the curve of excretion of the various components which were quantitated (Case V, Charts X and XI), but at the same time there is enough similarity in the different periods to justify the same conclusions as regards the ability of the kidney to

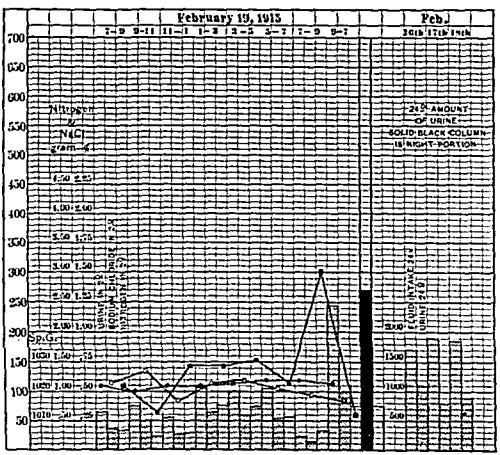


CHART IV, Case II.—The series of columns beginning at the left give the amount of urine, sodium chloride, and nitrogen in each two-hour portion from 7 A.M. to 9 P.M., and in the portion from 9 P.M. to 7 A.M. The solid lines joining dots in the space of each column give the specific gravity of the urine and the percentage concentration of sodium chloride and nitrogen. Next is indicated the night portion of urine in relation to the total twenty-four-hour amount. The columns at the right give the fluid intake and urine output in the days preceding the test day.

excrete the various components when no extraneous factors in the interval between the tests had come in to alter the character of the result.

Perhaps there has been a somewhat closer agreement between the two tests in regard to the salt excretion than has been found in the nitrogen excretion. It has been our experience that the ability of the kidney to excrete salt is decreased much earlier than is the case with nitrogen, and many more of our cases have shown an inability to excrete salt well than has been the case with the nitrogen. This

may possibly explain the greater variation in the results with the nitrogen in these cases which we have studied.

The cases with advanced nephritis, as judged by other tests and the general condition of the patient, by the Hedinger and Schlayer test diet show strikingly a tendency to fixation in the concentration of the urine as measured by the specific gravity, with a relatively slight variation in the amount passed in each two-hour period. In some cases this fixation in specific gravity has occurred at a low level (Chart VIII) and in others at a fairly high level (Chart IV). In the same way some patients have shown but slight variation in

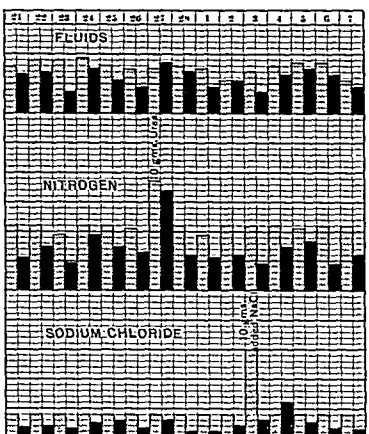


CHART V, Case II. — The hatched columns indicate intake; the solid columns output. The upper series are for fluids, the middle for nitrogen, and the lower for sodium chloride. The added salt and added urea are indicated by the lengthening of the columns of intake.

amount of their urine from period to period with either a very small amount or a fairly large amount in each period. Fixation of salt concentration has occurred in the more severe cases and usually at a low level of excretion. In the longer test, with added salt and added urea, the fixation of specific gravity and the lack of variation in the quantity of the urine is not so apparent.

The inability of the kidney to satisfactorily excrete salt is shown in both tests (Charts VI, VII, VIII, and IX). The same things are true with regard to the nitrogen (Charts VI, VII, VIII, and IX), though there has been less tendency to either fixation in the concen-

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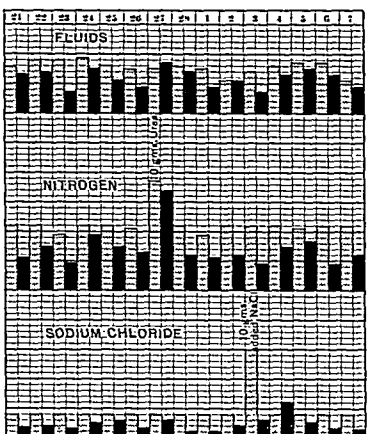


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tration of the nitrogen or constancy in the amount of nitrogen in each two-hour period.

Both forms of dietary renal tests are of limited application in the sense that cases of severe nephritis often are unable to take the diet on account of lack of appetite or developing nausea. In each form of test the amount of laboratory work is approximately the same. The only distinct advantage of the one over the other is in the shorter period required for the Hedinger and Schlayer test. It is to be

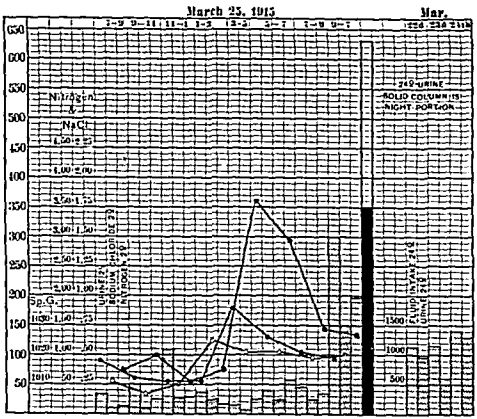


CHART VI, Case III.—The series of columns beginning at the left give the amount of urine, sodium chloride, and nitrogen in each two-hour portion from 7 A.M. to 9 P.M. and in the portion from 9 P.M. to 7 A.M. The solid lines joining dots in the space of each column give the specific gravity of the urine and the percentage concentration of sodium chloride and nitrogen. Next is indicated the night portion of urine in relation to the total twenty-four-hour amount. The columns at the right give the fluid intake and urine output in the days preceding the test day.

remembered that not exactly the same form of test is being applied, because in the one the chief factor in the test consists in seeing what the ability of the kidney is to excrete a single substance added to a diet containing only a moderate amount of that given substance along with other constituents. In the other test the excretion of several substances contained in a varying admixture of food constituents is being studied over a much shorter period of time. It might be that the results from the two kinds of tests would be more nearly comparable if in the longer test both added nitrogen and

added sodium chloride were introduced into the diet on the same day.

In the Hedinger and Schlayer test the results in a case of nephritis cannot be compared in any quantitative sense with what might be termed a normal curve of excretion. Normality consists with this diet in the ability to vary from period to period the amount of water, its specific gravity, the amounts of salt and nitrogen and their percentage concentration rather than to show any definite type of curve of excretion of each. Abnormality consists in a more or less degree of fixation in all of these values or in certain ones of them.

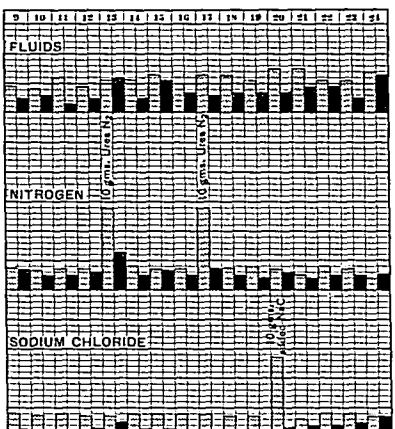


CHART VII, Case III.—The hatched columns indicate intake, the solid columns output. The upper series are for fluids, the middle for nitrogen, and the lower for sodium chloride. The added salt and added urea are indicated by the lengthening of the columns of intake.

Our general feeling has been that a study of the salt and nitrogen excretion by means of test diets is relatively of less use in determining the prognosis than are some of the other functional tests, such as the phenolsulphonephthalein excretion and the amount of blood nitrogen. This is not because the severe cases fail to show quite definite changes in their excretion, but because the other tests give fully as much information at a much less cost of labor and time. In the milder cases where phenolsulphonephthalein excretion is fair and blood nitrogen low in amount, disturbances in excretion of

water, salt, or nitrogen are found; the correct interpretation of this cannot be given until time enough has elapsed to show how these cases progress.

With regard to anatomical diagnosis, we think that a study of salt nitrogen, and water excretion will give very little aid. They serve to subdivide cases of chronic nephritis in a functional sense; the value of so subdividing the cases remains to be shown.

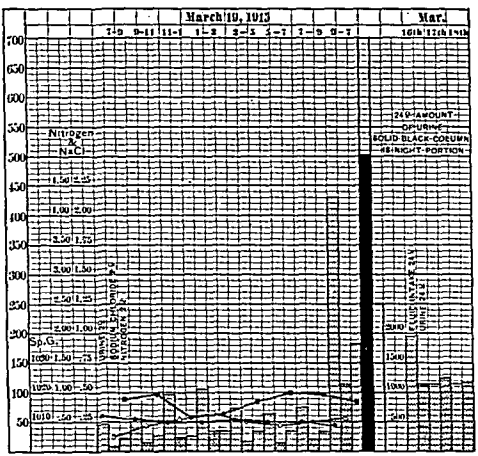


CHART VIII, Case IV.—The series of columns beginning at the left give the amount of urine, sodium chloride, and nitrogen in each two-hour portion from 7 A.M. to 9 P.M., and in the portion from 9 P.M. to 7 A.M. The solid lines joining dots in the space of each column give the specific gravity of the urine and the percentage concentration of sodium chloride and nitrogen. Next is indicated the night portion of urine in relation to the total twenty-four-hour amount. The columns at the right give the fluid intake and urine output in the days preceding the test day.

B. QUANTITATIVE STUDIES OF NON-PROTEIN NITROGENOUS BODIES OF THE BLOOD. In a series of eighteen patients (Charts XIII, XIV, and XV) with nephritis the total non-protein nitrogen of the blood was determined and also the ammonia nitrogen, urea nitrogen, uric acid nitrogen, creatinin, and combined creatinin and creatin nitrogen, and in most of the cases the amino-acid nitrogen. It was found in this series that the urea nitrogen increased usually in proportion as the total non-protein nitrogen increased and averaged 63.4 per cent. of the total. Ammonia nitrogen increased slightly as the total non-protein nitrogen rose, but this

rise was not proportional. Creatinin showed roughly a proportionate increase while amino-acid nitrogen showed no constant increase. Uric-acid nitrogen increased only very slowly, with an increase in total non-protein nitrogen, and the increase was not regular or proportionate to that of the total non-protein nitrogen. In those cases (14) in which amino-acids were quantitated the sum total of urea, ammonia, uric acid, creatinin, creatin, and amino-acid nitrogen was subtracted from the total non-protein nitrogen to give a figure for residual or unknown nitrogen. It has been

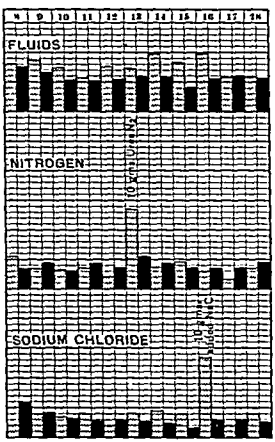


CHART IX. Case IV.—The hatched columns indicate intake, the solid columns output. The upper series are for fluids, the middle for nitrogen, and the lower for sodium chloride. The added salt and added urea are indicated by the lengthening of the columns of intake.

pointed out by others that such a nitrogen portion might contain the toxic element in nephritis, and so should be largest in those cases with most evident toxemia. In our figures it was roughly proportionate to the clinical severity of the case. However, it is quite evident that summation of errors in individual determinations may be responsible in part for the amount of residual nitrogen. Furthermore, if there is a marked retention of non-protein substances it is probable that other substances known to be non-toxic not quantitated in our work may have caused all this increase, and the figure means only what a rise in total non-protein nitrogen means.

In these same cases the total non-protein nitrogen and the urea nitrogen of the spinal fluid were determined. With the exception of two cases with anuria (*Cases VIII and IX, Chart XII*) the total non-protein nitrogen of the spinal fluid averaged about 25 per cent. lower than that in the blood, while the urea nitrogen in each had almost identical values. It would seem from this that urea is the only one of the nitrogenous bodies readily excreted into the spinal

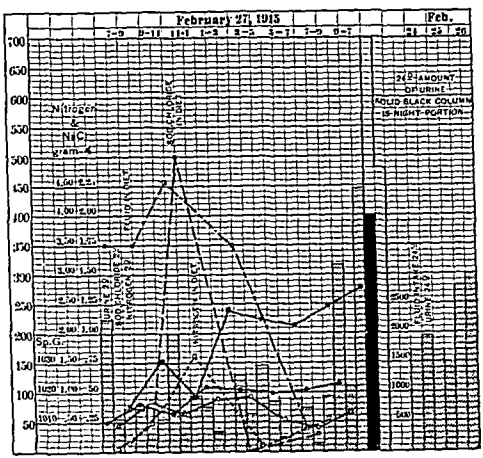


CHART X, Case V.—The series of columns beginning at the left give the amount of urine, sodium chloride, and nitrogen in each two-hour portion from 7 A.M. to 9 P.M., and in the portion from 9 P.M. to 7 A.M. The solid lines joining dots in the space of each column give the specific gravity of the urine and the percentage concentration of sodium chloride and nitrogen. Next is indicated the night portion of urine in relation to the total twenty-four-hour amount. The columns at the right give the fluid intake and urine output in the days preceding the test day. The broken lines joining dots indicate the amounts of fluid, sodium chloride, and nitrogen in each meal. In the case of nitrogen in the meals the scale is not the same as that of the nitrogen in the portions of urine, but is greater, corresponding to the scale in Chart I.

fluid, and that quantitation of spinal fluid nitrogen adds but little information to that obtained from quantitations of blood nitrogen. In all of these patients the condition of the retina was carefully studied. It was found that albuminuric retinitis occurred at any level of nitrogen retention, and there was no relation between its occurrence and the proportionate amount of any of the nitrogen bodies quantitated. Certainly, there was found no evidence of a

causal relation between any of these nitrogenous bodies and albuminuric retinitis.

C. DIURESIS IN RELATION TO DIURETICS. From our clinic have been published several papers on the effect of diuretic drugs on animals with experimental nephritis.[7] All together these have shown that the ordinary diuretics are either ineffectual or harmful to animals with these acute renal lesions. The results of these

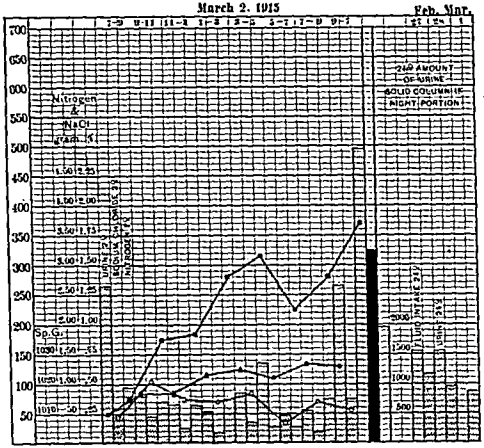


CHART XI. Case V.—The series of columns beginning at the left give the amount of urine, sodium chloride, and nitrogen in each two-hour portion from 7 A.M. to 9 P.M., and in the portion from 9 P.M. to 7 A.M. The solid lines joining dots in the space of each column give the specific gravity of the urine and the percentage concentration of sodium chloride and nitrogen. Next is indicated the night portion of urine in relation to the total twenty-four-hour amount. The columns at the right give the fluid intake and urine output in the days preceding the test day.

experiments have made us skeptical as to the benefit of diuretic drugs in human nephritis, and so we have been examining our records of patients to see if this skepticism was justified or not.

[7] Christian, Diuretic Drugs in Acute Experimental Nephritis, Jour. Amer. Med. Assoc., 1913, lxi, 267. Christian and O'Hare, A Study of the Therapeutic Value of a Diuretic (Theobromin Sodium Salicylate) in Acute Experimental Nephritis, Arch. of Int. Med., 1913, xi, 517. Walker and Dawson, The Effect of Diuretic Drugs on the Life of Animals with Severe Acute Nephritis, Arch. Int. Med., 1913, xii, 171. Christian, The Effect of Theobromin Sodium Salicylate in Acute Experimental Nephritis as Measured by the Excretion of Phenolsulphonephthalein, Arch. Int. Med., 1914, xiv, 829. Fitz, The Immediate Effect of Repeated Doses of Theobromin Sodium Salicylate and Theocin on Renal Function in Acute Experimental Nephritis, Arch. Int. Med., 1914, xiii, 945.

For some time it has been the routine custom on the medical service of the Peter Bent Brigham Hospital to measure and chart both the fluid intake and urine output of all patients. From these observations an idea may be obtained of diuresis in the average types of cases such as are admitted to a general hospital. Any patient in whom the urine output in twenty-four hours was 1600 c.c or over is regarded as having a diuresis; furthermore, any patient in whom the urine output in twenty-four hours exceeds the fluid intake is considered to have a diuresis. Diuresis in this sense

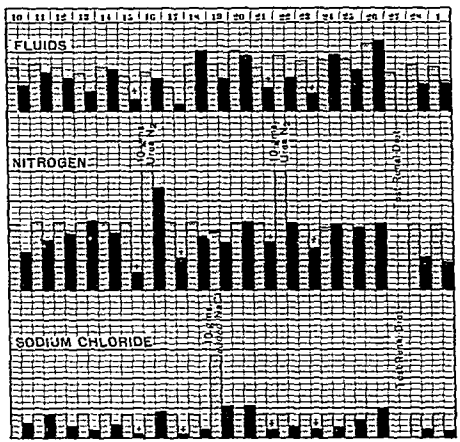


CHART XII. Case V.—The hatched columns indicate intake, the solid columns output. The upper series are for fluids, the middle for nitrogen, and the lower for sodium chloride. The added salt and added urea are indicated by the lengthening of the columns of intake.

occurred on at least one day in about 15 per cent. of 600 successive patients. Of the 89 patients among these 600 who showed diuresis, the largest group, 32, were cases of chronic cardiac disease, with decompensation in which, with digitalis, limitation of fluid intake and rest, diuresis followed. Next in order came cases of chronic nephritis, 22 in number. Diuresis in this group will be discussed more in detail later. Six patients had diabetes and seven typhoid; in both, diuresis was due to increased fluid intake. The others were miscellaneous cases in which it was often difficult to even surmise as to the direct cause of the diuresis. In this group are patients with diuresis during convalescence from pneumonia and from

CHART XIII.—TABLES SHOWING DETERMINATIONS OF NITROGENOUS BODIES IN BLOOD AND SPINAL FLUID IN CASES OF CHRONIC NEPHRITIS WITH NORMAL EYE-GROUNDS.

| No. | Hosp. Med. No. | Blood. Total non-protein nitrogen. | Urea nitrogen. | Ammonia nitrogen. | Uric acid nitrogen. | Creatinine nitrogen. | Creatine nitrogen. | Amino acid nitrogen. | Residual nitrogen. | Chlorides in gms. | Spinal fluid. Total non-protein nitrogen. | Urea nitrogen. | Blood pressure. | Phthalein excretion in 2 hours. | Remarks. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 2358 | 26.77 | 14.38 | 0.09 | 0.40 | 0.77 | 0.99 | 6.78 | 3.36 | 0.4476 | 17.85 | 11.09 | 130-85 | 48% | Normal control. |
| 2 | 2319 | 20.43 | 15.63 | 0.15 | 0.34 | 0.67 | 0.05 | 5.42 | 6.67 | 0.4435 | 24.68 | 15.45 | 240-160 | 47% | |
| 3 | 2367 | 35.70 | 18.49 | 0.10 | 0.07 | 0.67 | 0.95 | 8.44 | 6.38 | 0.4391 | 27.35 | 18.50 | 210-108 | 52% | Chronic myocarditis. |
| 4 | 2348 | 43.48 | 23.67 | 0.12 | 0.40 | 0.59 | 1.19 | 6.52 | 11.09 | 0.4707 | 35.70 | 21.25 | 185-95 | 52% | |
| 5 | 1902 | 55.30 | 38.98 | 0.14 | 0.67 | 3.07 | 4.27 | ..... | ..... | 0.5153 | ..... | ..... | 260-110 | 12% | |
| 6 | 1951 | 57.60 | 36.85 | 0.15 | 0.04 | 0.82 | 5.70 | ..... | ..... | 0.4290 | ..... | ..... | 235-115 | 21% | |
| 7A | 2006 | 95.27 | 66.66 | 0.15 | 0.04 | 3.68 | 2.89 | ..... | ..... | 0.5303 | ..... | ..... | 100-98 | Unreadable trace | |
| 7B | | 90.90 | 62.50 | 0.10 | 0.53 | 5.08 | 2.32 | 6.42 | 13.86 | 0.5682 | 66.66 | 60.24 | 190-100 | Unreadable trace | Mercury poisoning. |
| 8 | 2259 | 128.00 | 95.10 | 0.10 | 0.08 | 5.20 | 7.08 | 5.80 | 13.80 | 0.3429 | 128.00 | 95.21 | 130-80 | ..... | |
| 9 | 2174 | 138.10 | 79.76 | 0.24 | 1.67 | 4.00 | 4.37 | 16.32 | 31.05 | 0.4210 | 142.90 | 85.88 | 185-140 | Unreadable trace[a] | |

7A on December 12. 7B on December 17.

CHART XIV.—TABLES SHOWING DETERMINATIONS OF NITROGENOUS BODIES IN BLOOD AND SPINAL FLUID IN CASES OF CHRONIC NEPHRITIS HAVING ONLY VASCULAR CHANGES IN THE EYE-GROUNDS.

| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 10 | 2132 | 47.61 | 29.58 | 0.18 | 0.40 | 2.02 | 3.58 | 10.23 | 1.52 | 0.4500 | ..... | ..... | 265-140 | 33% | |
| 11 | 2202 | 71.43 | 43.07 | 0.11 | 0.06 | 1.71 | 2.19 | 6.50 | 17.28 | 0.5362 | 47.62 | 40.32 | 245-150 | 18% | 17 cells in spinal fluid |
| 12 | 2316 | 93.23 | 60.00 | 0.16 | 0.43 | 3.03 | 4.34 | 8.05 | 18.57 | 0.4640 | 60.00 | 60.16 | 213-124 | Unreadable trace | |

CHART XV.—TABLES SHOWING DETERMINATIONS OF NITROGENOUS BODIES IN BLOOD AND SPINAL FLUID IN CASES OF CHRONIC NEPHRITIS WITH MARKED ALBUMINURIC RETINITIS.

| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 13 | 2354 | 23.81 | 14.60 | 0.10 | 0.35 | 0.61 | 0.99 | 4.92 | 3.14 | 0.4243 | 20.00 | 12.50 | 285-160 | 28% | Apoplexy. |
| 14 | 2074 | 40.98 | 27.00 | 0.17 | 0.39 | 1.07 | 2.21 | 5.22 | 4.32 | 0.4490 | 33.28 | 23.32 | 160-130 | 10% | |
| 15A | 2043 | 54.05 | 32.14 | 0.12 | 0.40 | 2.74 | 2.74 | ..... | ..... | 0.4558 | 43.40 | 26.50 | 250-166 | 10% | |
| 15B | | 60.61 | 41.54 | 0.12 | 1.26 | 2.30 | 3.12 | 10.61 | 1.63 | 0.4735 | 40.58 | 31.25 | 250-160 | 10% | |
| 16A | 2108 | 55.55 | 29.35 | 0.09 | 0.60 | 2.03 | 1.59 | 9.44 | 11.85 | 0.4407 | 37.21 | 27.77 | 190-150 | 15% | 4 cells per cm. in spinal fluid. |
| 16B | | 47.54 | 25.50 | 0.15 | 0.08 | 2.45 | 3.66 | 6.56 | 8.24 | 0.3907 | 33.33 | 26.00 | 150-130 | 11% | Herpes zoster complicating uremia. 91 cells per cm. in spinal fluid. |
| 17A | 1882 | 102.30 | 113.80 | 0.20 | 0.02 | 8.01 | 14.39 | ..... | ..... | 0.4788 | 125.00 | 111.11 | 218-128 | Unreadable trace | 10 cells per cm. in spinal fluid. |
| 17B | | 206.66 | 166.45 | 0.21 | 2.78 | 7.85 | 7.06 | ..... | ..... | 0.5141 | 188.69 | 166.66 | 250-130 | Unreadable trace | Uremia. 23 cells per cm. in spinal fluid. |
| 18 | 1975 | 257.70 | 181.80 | 0.33 | 1.51 | 0.01 | 30.03 | ..... | ..... | 0.4752 | ..... | ..... | 208-152 | Unreadable trace | Uremia. |

15A on December 19. 15B on December 30. 16A on January 4. 16B on January 19. 17A on November 30. 17B on December 14.

[a] Phthalein estimation made three weeks previously at Massachusetts General Hospital.

attacks of bronchial asthma; patients with Hodgkin's disease, general carcinomatosis of the long bones, carcinoma of the head of the pancreas; pleurisy with effusion long after the pleural fluid had been removed mechanically; tabes in a patient requiring catheterization; meningitis; pernicious anemia following transfusion, migraine, etc.

In the records of successive patients as used above are included many records of individuals who were in the hospital for short periods of time in which only relatively few observations of fluid output were made; so our figures based on these 600 successive patients very likely give an incorrect idea of the frequency of diuresis, indicating that it is less common in the average hospital patient than is really the case. To avoid any error incident to very brief stay under observation, another series of successive records were gone over and all charts of patients who remained in the hospital not less than seven completed days were examined.

A series of 117 such were studied. Of these 69, or 59 per cent., on at least one day showed an output of urine in excess of 1600 c.c., or in excess of fluid intake; while 48, or 41 per cent., did not. In making this division the first day in the hospital is not included, as it often represents an incompleted twenty-four hours. Furthermore, the urinary excretion of the first day frequently is influenced by the excitement of admission to the hospital and by other extraneous factors. It is to be remembered in this connection that we have defined diuresis in a very limited way. In the figures just given numerous factors enter to make the number showing diuresis relatively large. For example, in twenty cases of this group on only one day did the urine exceed, and then but slightly, the fluid intake. This happened on days when for some reason or other the patient drank relatively little fluid, but the total urine on these days when it had exceeded the fluid intake was well below 1600 c.c. in amount. We think that these cases justly may be excluded from the group regarded as showing a diuresis. If this is done the number showing a diuresis represents 41 per cent. of the total. In a number of other cases urinary output was only once slightly above 1600 c.c., or in a long stay in the hospital only occasionally did the urine exceed the fluid intake. Going over the cases in this way there was a definite diuresis in relatively few of the cases, naturally slightly more than in the group in which were included cases in the hospital for only a short stay, but still proportionately a small number.

The analysis of the 600 successive cases given above indicated that chronic cardiac involvement, chronic nephritis, typhoid, and diabetes most often were the conditions in which diuresis occurred. The same conditions were found most commonly as the diagnosis in the patients of this second group showing diuresis. An examination of another group of 100 records in a way similar to the second series gave very similar figures.

The striking things in going over these cases have been the relative infrequency of diuresis even of only short duration in our hospital patients, and the lack aside from digitalis or large fluid intake of an easily assignable cause for such diuresis as occurred. It seemed that possibly a study of a group of cases of nephritis with relation to diuresis might throw some light on the question, inasmuch as this was the only group aside from cases of cardiac insufficiency in which diuresis occurred with any frequency. Consequently, 100 consecutive cases with chronic nephritis who had remained in the hospital not less than one week were examined.

Of these 100 cases of chronic nephritis, 51 showed no diuresis in the sense described above, while 49 had diuresis on at least 1 day. Almost all of the cases of chronic nephritis had hypertension, and 47 of them showed evidence of cardiac lesion diagnosed either as chronic myocarditis or chronic valvular lesion of some kind. This diagnosis of cardiac lesion was based on either definite evidence of cardiac decompensation or on electrocardiographic evidence of disturbance in myocardial function. Of the 100 cases of chronic nephritis, 43 received no diuretic therapy (increased fluid intake, digitalis, theocin, or similar drugs), and of these 12 showed a diuresis while 31 did not; 29 patients received digitalis; 17 with an ensuing diuresis, 12 without diuresis. Of the 17 cases in whom digitalis produced a diuresis, 14 showed very definite evidence of cardiac lesion, while in 2 cardiac decompensation was very probably present as they were cases with hypertension with signs of edema at the bases of the lungs as well as subcutaneous edema. In the one remaining case of this group there was a normal blood-pressure and no signs of cardiac lesion and no physical findings to suggest cardiac decompensation. In 8 patients a large fluid intake resulting from thirst caused diuresis. In three patients given sodium bicarbonate it appeared to cause diuresis. In 4 patients on a standard nephritic diet, diuresis occurred when either 10 grams of sodium chloride or 20 grams of urea were added to the diet. Particularly interesting are 10 cases in which such diuretic drugs as theobromin sodium salicylate, potassium citrate, caffein, and theocin produced no diuresis.

Curiously enough, in the 100 cases of chronic nephritis these so-called diuretic drugs failed very generally to produce diuresis when used alone. Occasionally when they had been used in conjunction with digitalis there was a diuresis, and here the digitalis alone may have been the cause of the diuresis. The number of cases is, of course, too small to justify the conclusion that this group do not act as diuretics in the condition of chronic nephritis, but these findings justify further our feeling of skepticism, and we hope that they will stimulate renewed study of the problem of the action of diuretics.

Most of the patients in this group had slight if any edema. Possibly this is the cause of so many failures to obtain diuresis in

cases without cardiac failure. If so, then diuretic drugs would seem to have little value as eliminants of toxic substances in chronic nephritis without edema. Further evidence certainly is needed on this point to justify the use of diuretics in uremic conditions without edema in view of the evidence which has been accumulated

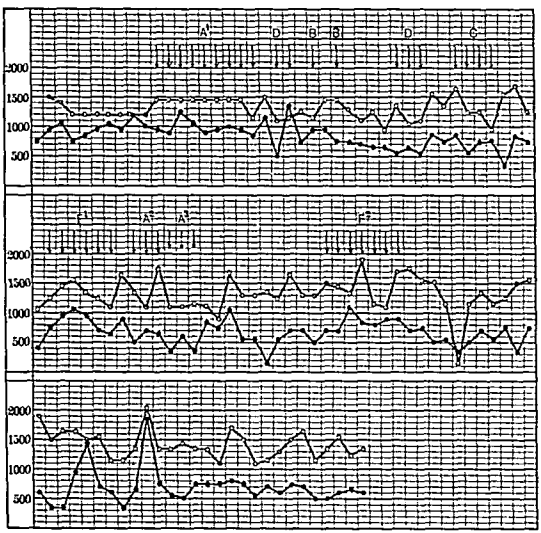


CHART XVI.—The solid black dots indicate the twenty-four-hour amount of urine in cubic centimeters. The black circles indicate the twenty-four-hour amount of fluid intake in cubic centimeters. Each arrow under $A^1$ indicates a day on which the patient received three doses of 0.1 gm. each of powdered digitalis leaves; under $A^2$ a day on which the patient received two doses of the same, and under $A^3$ a day on which the patient received two doses of 0.05 gm. each of powdered digitalis leaves. Each arrow under B indicates a dose of 0.5 gm. of theocin; under C a day on which the patient received 0.13 gm. of caffein citrate every four hours; under D a dose of 0.5 gm. of theobromin sodium salicylate; under $F^1$ a dose of 1 gm. of potassium citrate, and under $F^2$ a day on which the patient received two doses of 0.5 gm. each of potassium citrate.

that the diseased kidney is abnormally sensitive to fatigue and that diuretics may cause fatigue and consequent decrease in renal excretion, while in animals with acute lesions they are often demonstrably harmful. However, diuretic drugs do not have even any very constant effect in cases of nephritis with edema and without cardiac decompensation, as is shown by the following cases:

A boy, aged nineteen years (Peter Bent Brigham Hospital, Medical No. 1225, Chart XVI and XVII), came into the hospital complaining that for about a week he had had edema of his legs, abdomen, back, and cheeks. When he came in his blood-pressure was 160 mm. of mercury. There was evidence of a moderate amount of fluid in his abdomen and in his thorax, and there was the edema of the subcutaneous tissue of which he complained. There was a slight degree of exudation in the retina of one eye. His urine

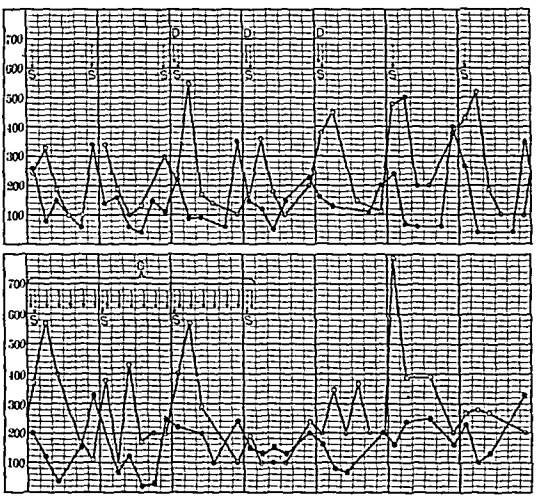


CHART XVII.—The solid black dots indicate the four-hour amount of urine in cubic centimeters. The black circles indicate the four-hour amount of fluid intake in cubic centimeters. Each arrow under C indicates one dose of 0.13 gm. of caffein citrate, and under D indicates a dose of 0.5 gm. of theobromin sodium salicylate. Each arrow over S indicates an electric light sweat bath in bed.

contained a large amount of albumin, many cellular and granular casts, and a few red-blood cells. His phenolsulphonephthalein excretion in two hours was 34 per cent. His total non-protein nitrogen was 35 mgm. per 100 c.c. of blood. He came into the hospital on May 20 and remained until September 9. During this time his phenolsulphonephthalein excretion fluctuated between the figure given above and a minimum figure of 15 per cent. in two hours; whereas his blood nitrogen fluctuated between 35 mgm. and

44 mgm. per 100 c.c. of blood, with one reading of 71 mgm. per 100 c.c. of blood at a time when there was no other evidence of increased renal insufficiency. During his stay in the hospital the amount of albumin in his urine gradually decreased in amount, and the edema in various parts of his body all disappeared. As shown by the appended chart (Chart XVI); theocin, theobromin sodium salicylate, caffein citrate, potassium citrate, and digitalis all failed to produce any diuresis, as shown by the twenty-four-hour amount of urine in relation to the fluid intake. It was thought possible that in this case the drugs might have produced an immediate diuresis which was offset by subsequent fall in excretion. To see whether or not this was the case, the patient's urine was collected in four-hour periods for fourteen days, but as shown by the chart (Chart XVII) there was no evidence of diuresis of this type

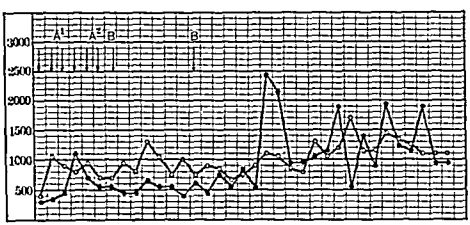


CHART XVIII.—The solid black dots indicate the twenty-four-hour amount of urine in cubic centimeters. The black circles indicate the twenty-four-hour amount of fluid intake in cubic centimeters. Each arrow under $A^1$ indicates a day on which the patient received three doses of 0.1 gm. each of powdered digitalis leaves; under $A^2$ a day on which the patient received two doses of 0.05 gm. each of powdered digitalis leaves. Each arrow under B indicates a dose of 0.3 gm. of theocin.

In another patient, aged thirty-eight years (Peter Bent Brigham Hospital, Medical No. 1754, Chart XVIII), single doses of theocin seemed to produce no effect. This patient came into the hospital on October 11 and remained until November 15. He noticed eleven days before coming in, that his legs began to swell, and five days before he came in that his face was swollen; two days before he came in the edema had involved his genitalia. This patient had a normal blood-pressure, signs of fluid in his thorax, possibly some fluid in his abdomen, and a marked degree of subcutaneous edema. When he came in his urine contained a large amount of albumin, many hyalin and granular casts, many of which had fat attached, but very few red blood cells. His excretion of phenolsulphonephthalein was 28 per cent. in two hours. His non-protein nitrogen was 36 mgm. per 100 c.c. of blood. During his stay in the hospital his blood nitrogen decreased to 24 mgm. per 100 c.c. of blood, and

his phenolsulphonephthalein excretion increased to 39 per cent. The albumin in his urine decreased in amount and the casts decreased

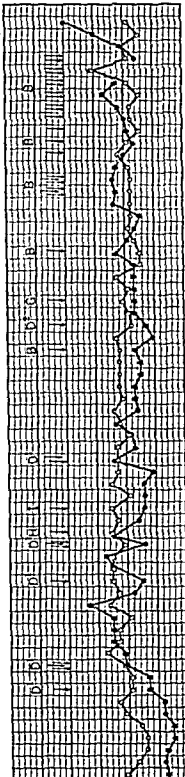


CHART XIX.—The solid black dots indicate the twenty-four-hour amount of urine in cubic centimeters. The black circles indicate the twenty-four-hour amount of fluid intake in cubic centimeters. Each arrow under B indicates a dose of 0.3 gm. of theocin; under D a dose of 0.25 gm. of theobromin sodium salicylate; under D' a dose of 0.5 gm. of theobromin sodium salicylate; under G removing 2050 c.c. of ascitic fluid; under H 20 gm. of urea, and under I, 10 gm. of sodium chloride.

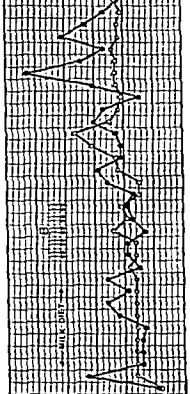


CHART XX.—The solid black dots indicate the twenty-four-hour amount of urine in cubic centimeters. The black circles indicate the twenty-four-hour amount of fluid intake in cubic centimeters. Each arrow under B indicates a dose of 0.3 gm. of theocin.

in numbers. Chart XVIII shows the lack of effect of digitalis and theocin and a subsequent diuresis on two days for which no cause could be assigned.

Another patient of similar type, aged thirty-one years (Peter Bent Brigham Hospital, Medical No. 1524, Chart XIX), was in the hospital from September 10 to November 18. Swelling of his legs developed about three and a half months before he came in. When he came to the hospital he showed considerable edema of his legs and trunk, with definite signs of fluid in his abdomen. His phenolsulphonephthalein excretion varied between 28 per cent. and 52 per cent. in two hours. His non-protein nitrogen was 23 mgm. per 100 c.c. of blood. His urine picture was essentially the same as in the preceding patient. His blood-pressure was 150 mm. of mercury. In this patient, as shown by the chart (Chart XIX), theobromin sodium salicylate and theocin each appeared to produce a slight though not constant diuresis.

A fourth patient, aged thirty-five years (Peter Bent Brigham Hospital, Medical No. 1879, Chart XX), was in the hospital from November 7 to December 12 with a history that three days before entrance his feet had begun to swell and he had some dyspnea. This was preceded about a week and a half before by nausea, with some vomiting. When he came into the hospital he had marked edema of his feet and lower legs with many coarse rales in his lungs. His blood-pressure varied between 140 and 190 mm. of mercury. His phenolsulphonephthalein output varied between 30 per cent. and 46 per cent. in two hours, and his blood nitrogen between 50 and 82.5 mgm. per 100 c.c. of blood. His urine showed a large trace of albumin, hyalin, and finely and coarsely granular casts.

On a diet of 800 c.c. of milk and no added fluid he had a moderate diuresis (Chart XX). He was then put on theocin, 0.3 gm. twice a day, from November 18 to November 22, during which period his diuresis was rather less than it had been previously. His edema had to a considerable extent disappeared. After theocin was stopped there was a slight temporary diuresis. Then on a larger intake of fluid slight edema developed. With a reduction in the fluid and the patient back in bed there was quite definite diuresis, as shown by the chart, though he received no drug treatment.

A fifth patient, aged forty-five years (Peter Bent Brigham Hospital, Medical No. 1885, Chart XXI), was in the hospital from November 9 to December 9, with a story that seven months before admission he had had pneumonia, and this had been accompanied by edema of his lower extremities, which a little later increased so that it involved his genitalia, and his abdomen began to swell. In another hospital this edema disappeared, but returned about four months ago shortly after discharge from that hospital. It remained small in amount, however, until about two weeks before admission to the Brigham Hospital, when it markedly increased. He also

began to have nausea and vomiting. When he came into the hospital he had signs of ascites, edema of the legs, scrotum, and abdominal wall. His heart showed the physical signs of aortic and mitral insufficiency. His blood-pressure varied between 150 and 210 mm. of mercury. His phenolsulphonephthalein output varied between 22 per cent. and 33 per cent. in two hours, and his blood nitrogen between 37.5 and 39 mgm. per 100 c.c. of blood. His urine showed essentially the same picture as the preceding case.

When he first came into the hospital he was put on a diet of 800 c.c. of milk, with no added fluids. On November 15 he was put on a salt-free diet. On November 17 he was given 0.3 gm. of theocin twice, and on November 18 and November 19 he was given the same amount of theocin at 8 P.M. without any diuresis (Chart XXI). On November 22, 3700 c.c. of fluid were removed from his abdomen. Finally, on November 27, he was put on small doses of digitalis twice a day, with a definite diuresis.

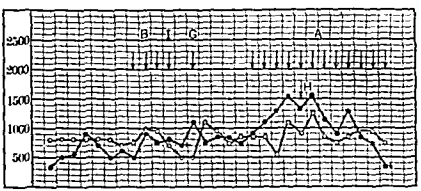


CHART XXI.—The solid black dots indicate the twenty-four-hour amount of urine in cubic centimeters. The black circles indicate the twenty-four-hour amount of fluid intake in cubic centimeters. Each arrow under A indicates a day on which the patient received two doses of 0.05 gm. of powdered digitalis leaves; under B a dose of 0.3 gm. of theocin; under G a day on which 3700 c.c. of ascitic fluid was removed; under H, 20 gm. of urea and under I, 10 gm. of sodium chloride.

That diuretic drugs are not always ineffectual is well shown by a cardiac case with aortic stenosis and insufficiency who was in the hospital from January 23 to March 21 (Peter Bent Brigham Hospital, Medical No. 2212, Charts XXII and XXIII) with marked edema. As shown by the chart (Chart XXII), theocin in connection with digitalis produced a marked diuresis, though theobromin sodium salicylate did not have the same result. With the theocin, however, he became markedly nauseated. It was thought that this difference in action might be due to differences in absorption of the two drugs. To determine this they were given intravenously at a later period during a second stay in the hospital and in the same relation to digitalis. The same difference in action was apparent after intravenous dosage; theocin produced a striking diuresis, as shown by the chart (Chart XXIII), while theobromin sodium salicylate produced a very slight increase in urine output.

Interestingly, nausea again occurred, though to a less extent, than when the drugs were given by mouth.

These several results seem to justify our skepticism in regard to the use of diuretics. Certainly more information is needed

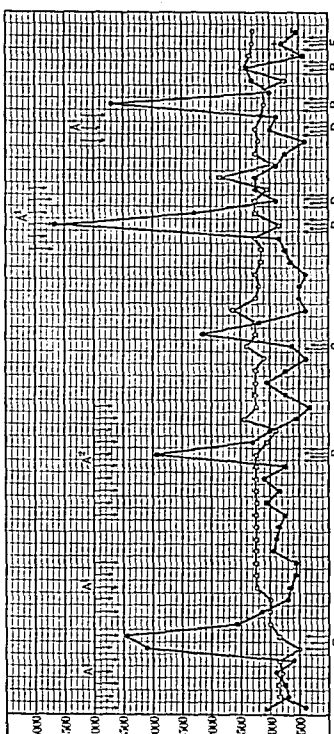


CHART XXII.—The solid black dots indicate the twenty-four-hour amount of urine in cubic centimeters. The black circles indicate the twenty-four-hour amount of fluid intake in cubic centimeters. Each arrow under A¹ indicates a day on which the patient received three doses of 10 c.c. each of an infusion of digitalis. Each arrow under A² indicates a day on which the patient received two doses of 10 c.c. each of an infusion of digitalis. Each arrow over B indicates one dose of 0.5 gm. of theocin. Each arrow over C indicates one dose of 0.2 gm. of caffein sodium benzoate. Each arrow over D indicates one dose of 0.3 gm. of theobromin sodium salicylate. Each arrow over E indicates one dose of 0.5 gm. of theocin sodium acetate.

before we can employ diuretics efficiently in cases of renal or cardio-renal disease.

D. FUNCTIONAL TESTS IN RELATION TO ANATOMICAL CHANGES IN THE KIDNEY. Up to the present time 18 cases of chronic nephritis have come to autopsy at the Brigham Hospital upon which enough

clinical work had been done to make a comparison between the clinical and anatomical findings of interest. Most of these cases were seriously ill when they were admitted to the hospital, and consequently could not be put upon standard diets to which were added salt and urea to determine the relative ability of the kidney to excrete salt and nitrogen. Determinations of phenolsulphonephthalein excretion and estimations of the non-protein nitrogen in the blood were made, and, in addition, careful general clinical examinations were carried out.

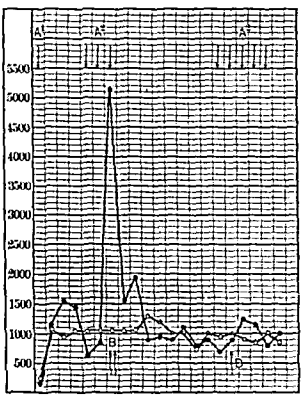


CHART XXIII.—The solid black dots indicate the twenty-four-hour amount of urine in cubic centimeters. The black circles indicate the twenty-four-hour amount of fluid intake in cubic centimeters. The arrow under $A^1$ indicates a subcutaneous dose of 1 c.c. of digipuratum and under $A^2$ a day on which the patient received three doses of 10 c.c. each of an infusion of digitalis. The arrows at B indicate two doses of 0.5 gm. each of theocin given intravenously and at D a dose of 1 gm. of theobromin sodium salicylate given intravenously.

In the 18 cases, microscopic study of the kidney showed a chronic vascular nephritis, in the sense used by Mallory in his recent book, in 14 cases, and in 4 cases the lesion was a chronic glomerular nephritis. The study of blood nitrogen, phenolsulphonephthalein excretion, and the excretion in the urine of albumin and casts did not give results during life which justified a definite diagnosis in the anatomical sense on many of these cases. In other words, during life it was not possible to accurately foretell what histological changes would be found in the kidneys in those patients who were studied in the last stages of a chronic nephritis. The clinical study of those cases has given much evidence of use in regard to prognosis. In

a functional sense it has been possible to classify the cases into various groups, but it has not been possible to diagnose accurately the anatomical condition of the kidney. As has already been said, test renal meals and test diets could not be applied in these cases. Whether a more satisfactory anatomical diagnosis could have been made if these had been carried out is merely a matter of speculation.

It is hoped that as time goes on cases which we have studied in the earlier stages will return to the hospital for repeated examinations as their disease progresses, and in the last stages may be under observation. If autopsies can be obtained when such patients die, an opportunity will be afforded to compare the results of functional studies with end anatomical conditions. It is only in the earlier stages of the nephritis that satisfactory dietary studies can be made as well as other methods of estimating renal function. Until this happens it will not be possible to say how far an accurate anatomical diagnosis can be made during life. We feel sure that such functional studies as can be made in the late stages of chronic nephritis do not make possible an accurate anatomical diagnosis, because at this stage almost all parts of the renal function are at a low level of efficiency.

## CONCLUSIONS.

A. Test Renal Meals in Relation to Renal Function. 1. Of two general methods used the v. Monakow standard diet with days of added salt or urea and the Hedinger and Schlayer test day on a mixed diet, the first requires about ten days of hospital study and the second three days. Using the two methods on a series of patients we have obtained very similar results by each.

2. Though similar the results are not quantitatively identical. The same is true for the same test repeated several times on the same patient.

3. For the Hedinger and Schlayer test there is no constant normal curve of excretion. Normality consists in the ability to vary from period to period the amounts and concentration of the substances quantitated. Abnormality consists in a more or less marked degree of fixation in all of these values from period to period.

4. Fixation in excretion of nitrogen seems to develop at a later period in most cases than is true for water and salt.

B. Quantitative Studies of Non-protein Nitrogenous Bodies of the Blood. 1. Urea nitrogen in a series of cases averaged 63.4 per cent. of the total non-protein nitrogen of the blood, and its increase was usually proportionate to the increase of the total non-protein nitrogen.

2. Ammonia nitrogen increased slightly but not proportionately. The same held for uric acid and amino-acid nitrogen.

3. Creatinin showed roughly a proportionate increase.

4. The difference between determined forms of nitrogen and total non-protein nitrogen was greatest in cases with clinically most severe symptoms.

5. In the spinal fluid the increase in nitrogen is almost solely in urea nitrogen except in cases of anuria.

6. We can see no advantage in quantitating the nitrogen of the spinal fluid over quantitating it in the blood.

7. No relationship existed between the amount of non-protein nitrogen in the blood and changes in the retina.

C. Diuresis in Relation to Diuretics. 1. Diuresis is relatively infrequent in the average hospital patient.

2. Except for diuresis in cardiac cases following digitalis, diuresis bears an inconstant relation to diuretic drugs.

3. In cases of nephritis with or without edema and without cardiac decompensation, diuretic drugs more often fail to produce a diuresis than the reverse.

4. In cardiorenal cases, diuretic drugs often produce a striking diuresis.

5. Our observations justify a healthy skepticism as to the efficacy of diuretic drugs in cases of nephritis without cardiac decompensation.

D. Functional Tests in Relation to Anatomical Changes in the Kidney. 1. In 18 cases of chronic nephritis dying and coming to autopsy no constant relations have been found between anatomical lesions and renal function insofar as excretion of phenolsulphonephthalein, albumin in the urine, casts, presence or absence of edema, blood-pressure determinations, etc., are concerned.

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## STUDIES IN MONILIASIS OF THE DIGESTIVE TRACT IN PORTO RICO.[1]

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In April, 1913, I wrote a paper[2] for the Tenth Annual Meeting of the American Society of Tropical Medicine, entitled "Notes on Sprue in Porto Rico, and the Results of Treatment by Yellowed Santonin," announcing the presence of that disease in the island. The paper was the outcome of a clinical study of 86 cases extending

[1] Read before the Association of American Physicians, May 11, 12 and 13, 1915, in Washington, D. C.

[2] Am. Jour. of Trop. Dis. and Prevent. Med., 1913, I, 146.